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Neurological Dysfunction in Coronavirus Disease-19 (COVID-19)

From:
Arshed Hussain Parry, MD, Abdul Haseeb Wani, MD, Mudasira Yaseen, MD

From the Department of Radiodiagnosis, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India (A.H.P.); Department of Radiodiagnosis, Government Medical College, Srinagar, Jammu & Kashmir, India (A.H.W.); Department of Anesthesiology and Critical Care Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India (M.Y.).

Neurological dysfunction has been reported to occur in up to 36.4% patients of coronavirus disease-19 (COVID-19) and patients with severe infection are more likely to develop neurological manifestations (1). The most common reported symptoms include altered mental status, headache, neurodeficit, dizziness, and seizures. The symptoms attributable to cranial nerve dysfunction including anosmia, dysguesia, nerve pain, and Miller-Fisher syndrome have also been reported (1,2). Neuroimaging in symptomatic cases of COVID-19 has revealed various patterns of brain injury. Large territory ischemic infarcts involving branches of circle of Willis, lacunar infarcts, cerebral venous thrombosis, subdural hemorrhage, and intraparenchymal hemorrhage have been reported. Diffuse cerebral and less commonly cerebellar white matter hyperintensity on T2-weighted and Fluid-Attenuated Inversion Recovery Sequence MRI suggestive of demyelination or leukoencephalopathy have been reported along with microhemorrhages in the white matter of brain (3).

The exact underlying mechanisms of brain injury in COVID-19 are not known at present. However, the following putative mechanisms in various combinations may explain the broad range of patterns of brain injury in COVID-19.

HYPERCOAGULABILITY

Coagulation dysfunction, increasingly being reported in severe COVID-19 may precipitate large vessel strokes, dural venous thrombosis, or intracranial hemorrhage.

VASCULAR INJURY

Vascular injury may result from two mechanisms. It may result from tropism of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) for endothelial cells which express angiotensin-converting enzyme 2 (ACE2), the target receptor for SARS-CoV-2. SARS-CoV-2-induced endothelial damage may predispose to in situ cerebral vascular thrombosis or may lead to disruption of blood brain barrier (BBB). Disruption of BBB causes increased permeability of capillaries with consequent cerebral edema or microhemorrhages. Alternately, vascular damage may be caused by infection induced vasculitis or vasculopathy (as is seen in varicella zoster virus or HIV) (4).

HYPOXIA

Hypoxic brain damage in severe COVID-19 may explain few of the neuroimaging findings in these patients. Acute hypoxemia may result in hypoxic ischemic encephalopathy. Prolonged hypoxia may induce demyelination or produce white matter microhemorrhages. Prolonged hypoxemia leads to oligodendroglial cell injury. Oligodendroglial cells constitute the myelin sheath of nerve cells and their death causes demyelination of white matter of brain. Prolonged hypoxia also causes BBB disruption leading to leaky capillaries which can produce microhemorrhages.

NEUROTROPISM

SARS-CoV-2 spike protein S1 has an avid affinity for the human ACE2 receptors, which are expressed on neurons. This neurotropism of SARS-CoV-2 can lead to direct brain injury. Neurologic injury has been reported in the other coronavirus infections like SARS and Middle East Respiratory Syndrome in the past with nucleic acid of these coronaviruses retrieved in the cerebrospinal fluid of infected patients and also in their brain tissue on autopsy, suggesting neurotropism and direct damage as the underlying mechanism of brain injury (4). Virus may reach brain through hematogenous route or retrograde axonal transport (via the olfactory nerve).

IMMUNE-MEDIATED INJURY

Cranial nerve dysfunction like Miller-Fisher Syndrome and polyneuritis cranialis reported in COVID-19 may result from an aberrant immune response to COVID-19 in some cases.

PRO-INFLAMMATORY STATE

Infection has the potential to trigger ischemic strokes and up to a third of ischemic strokes are preceded by infection (5). Infection can precipitate stroke through a range of potential mechanisms. Rupture of vulnerable atherosclerotic plaques in the presence of severe pro-inflammatory state may lead to thromboembolic events in severe COVID-19 (5). The massive release of cytokines in severe COVID-19 infection may result in breakdown of the BBB predisposing to brain injury.

DYSELECTROLYTEMIA

Hypokalemia and hyponatremia are commonly seen in patients with severe COVID-19, with a correlation with the degree of renal injury. Hyponatremia causes diffuse brain

edema whereas rapid correction of hyponatremia is linked to demyelination.

Attempts to isolate SARS-CoV-2 from cerebrospinal fluid and autopsies of the COVID-19 victims may shed light on the mechanism of brain injury.

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